# Final Progress Report for Research Projects Funded by Health Research Grants

Instructions: Please complete all of the items as instructed. Do not delete instructions. Do not leave any items blank; responses must be provided for all items. If your response to an item is "None", please specify "None" as your response. "Not applicable" is not an acceptable response for any of the items. There is no limit to the length of your response to any question. Responses should be single-spaced, no smaller than 12-point type. The report **must be completed using MS Word**. Submitted reports must be Word documents; they should not be converted to pdf format. Questions? Contact Health Research Program staff at 717-783-2548.

1. **Grantee Institution:** Drexel University

2. **Reporting Period (start and end date of grant award period):** 1/1/2009-12/31/2010

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** Anne Martella

4. **Grant Contact Person's Telephone Number:** (215) 895-6471

5. **Grant SAP Number:** 4100047631

6. **Project Number and Title of Research Project:** 4 - *A Microfluidic Model of Drug-induced Liver Toxicity* -

7. **Start and End Date of Research Project:** 1/1/2009-12/31/2010

8. **Name of Principal Investigator for the Research Project:** Michael Bouchard, PhD

9. **Research Project Expenses**.

   9(A) Please provide the amount of health research grant funds spent on this project for the entire duration of the grant, including any interest earned that was spent:

   $ $103,403

   9(B) Provide the last names (include first initial if multiple individuals with the same last name are listed) of **all** persons who worked on this research project and were supported with health research funds. Include position titles (Principal Investigator, Graduate Assistant, Post-doctoral Fellow, etc.), percent of effort on project and total health research funds expended for the position. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

| Last Name | Position Title | % of Effort on Project | Cost |
|---|---|---|---|
| Siddhartha Rawat | Graduate Assistant | 100% | $28,946 |
| Simon Cocklin | Assistant Research Professor | 12.5% | $10,741 |
| Michael Bouchard | Principal Investigator | 5% | $ 8,928 |

9(C) Provide the names of **all** persons who worked on this research project, but who *were not* supported with health research funds. Include position titles (Research Assistant, Administrative Assistant, etc.) and percent of effort on project. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

| Last Name | Position Title | % of Effort on Project |
|---|---|---|
| Joseph Cirillo | Graduate Assistant | 50% |
| Moses Noh | Associate Professor | 5% |

9(D) Provide a list of **all** scientific equipment purchased as part of this research grant, a short description of the value (benefit) derived by the institution from this equipment, and the cost of the equipment.

| Type of Scientific Equipment | Value Derived | Cost |
|---|---|---|
| None | | |

**10. Co-funding of Research Project during Health Research Grant Award Period.** Did this research project receive funding from any other source during the project period when it was supported by the health research grant?

Yes__x__ No_____

If yes, please indicate the source and amount of other funds:

There was a three-month overlap at the end of the Health Research Grant Award Period and the beginning of the R21 NIH grant entitled: "A Microfluidic-platform Mini-Liver System for Human Liver Biology Studies". There was no overlap with paid personnel.

**11. Leveraging of Additional Funds**

11(A) As a result of the health research funds provided for this research project, were you able to apply for and/or obtain funding from other sources to continue or expand the research?

Yes_____X____ No_____

If yes, please list the applications submitted (column A), the funding agency (National Institutes of Health—NIH, or other source in column B), the month and year when the application was submitted (column C), and the amount of funds requested (column D). If you have received a notice that the grant will be funded, please indicate the amount of funds to be awarded (column E). If the grant was not funded, insert "not funded" in column E.

Do not include funding from your own institution or from CURE (tobacco settlement funds). Do not include grants submitted prior to the start date of the grant as shown in Question 2. If you list grants submitted within 1-6 months of the start date of this grant, add a statement below the table indicating how the data/results from this project were used to secure that grant.

| A. Title of research project on grant application | B. Funding agency (check those that apply) | C. Month and Year Submitted | D. Amount of funds requested: | E. Amount of funds to be awarded: |
|---|---|---|---|---|
| A Microfluidic-platform Mini-Liver System for Human Liver Biology Studies | ☒NIH<br>☐ Other federal (specify:_____)<br>☐ Nonfederal source (specify: _____) | 5/2010 | $275,000 | $275,000 |

11(B) Are you planning to apply for additional funding in the future to continue or expand the research?

Yes___X_____ No_____

If yes, please describe your plans:

We will use a combination of the data acquired from the studies outlined here and those associated with the R21 NIH grant to apply for an R01 and an NSF grant. These grants will continue the collaboration between Dr. Moses Noh and Dr. Michael Bouchard and use the mini-liver model systems to address whole-liver questions that cannot be effectively addressed in current model systems. For example, because we will be able to control the local oxygen and fluidic environment, we can begin to address the consequences of "zonation" in the liver as well as the direct impact of oxygen and fluid flow on hepatocyte physiology. In addition, the expansion of these studies to a microfabricated human liver system will allow studies in human liver cells that are maintained over longer periods of time than current system for culturing human hepatocytes. The use of smaller amounts of human cells in the microchannels will enable better use of the limited supply of available primary human liver cells. We will propose to use these systems as new models for studying hepatitis virus infections of the liver as well as hepatocyte responses to drugs or alcohol.

**12. Future of Research Project.** What are the future plans for this research project?

As described above, we plan to use the system generated with primary rat liver cells to study the effect of hepatitis virus replication as well as drug and alcohol exposure on hepatocyte and liver sinusoidal endothelial cell physiology when these cells are maintained in an environment that more accurately mimics the in vivo environment. We are also expanding this model and systematically replacing each of the rat primary liver cell types with human primary liver cells to generate a new model system that mimics the in vivo microarchitecture and microenvironment of the human liver. In recent studies, we have been able to maintain human hepatocytes for at least 15 days in the microchannels; this extends the proof-of-concept provided by the rat system. The human system will be used as a novel model to study the direct effect of a hepatitis B virus infection or alcohol or drug exposure on the human liver.

**13. New Investigator Training and Development**. Did students participate in project supported internships or graduate or post-graduate training for at least one semester or one summer?

Yes____X_____ No_____

If yes, how many students? Please specify in the tables below:

| | Undergraduate | Masters | Pre-doc | Post-doc |
|---|---|---|---|---|
| Male | | | 2 | |
| Female | | | 1 | |
| Unknown | | | | |
| **Total** | | | **3** | |

| | Undergraduate | Masters | Pre-doc | Post-doc |
|---|---|---|---|---|
| Hispanic | | | | |
| Non-Hispanic | | | 2 | |
| Unknown | | | 1 | |
| **Total** | | | **3** | |

| | Undergraduate | Masters | Pre-doc | Post-doc |
|---|---|---|---|---|
| White | | | 1 | |
| Black | | | | |
| Asian | | | 2 | |
| Other | | | | |
| Unknown | | | | |
| **Total** | | | **3** | |

**14. Recruitment of Out-of–State Researchers**. Did you bring researchers into Pennsylvania to carry out this research project?

Yes_____ No____X_____

If yes, please list the name and degree of each researcher and his/her previous affiliation:

**15. Impact on Research Capacity and Quality**. Did the health research project enhance the quality and/or capacity of research at your institution?

Yes_____ No_____X_____

If yes, describe how improvements in infrastructure, the addition of new investigators, and other resources have led to more and better research.

**16. Collaboration, business and community involvement.**

16(A) Did the health research funds lead to collaboration with research partners outside of your institution (e.g., entire university, entire hospital system)?

Yes___X_____ No_____

If yes, please describe the collaborations:

These funds have enhanced the collaboration between Dr. Moses Noh, an Associate Professor in the Department of Mechanical Engineering and Mechanics at Drexel University with Dr. Michael Bouchard in the Department of Biochemistry and Molecular Biology in the Drexel University College of Medicine. This collaboration, and the expertise that each researcher brings to this project, was seen as one of the strengths that facilitated receiving an NIH R21 grant to continue these studies.

16(B) Did the research project result in commercial development of any research products?

Yes_____ No____X_____

If yes, please describe commercial development activities that resulted from the research project:

16(C) Did the research lead to new involvement with the community?

Yes_____ No_____X_____

If yes, please describe involvement with community groups that resulted from the research project:

**17. Progress in Achieving Research Goals, Objectives and Aims.**

List the project goals, objectives and specific aims (as contained in the grant application's strategic plan). Summarize the progress made in achieving these goals, objectives and aims for the entire grant award period. Indicate whether or not each goal/objective/aim was achieved; if something was not achieved, note the reasons why. Describe the methods used. If changes were made to the research goals/objectives/aims, methods, design or timeline since the original grant application was submitted, please describe the changes. Provide detailed results of the project. Include evidence of the data that was generated and analyzed, and provide tables, graphs, and figures of the data. List published abstracts, poster presentations and scientific meeting presentations at the end of the summary of progress; peer-reviewed publications should be listed under item 20.

This response should be a DETAILED report of the methods and findings. It is not sufficient to state that the work was completed. Insufficient information may result in an unfavorable performance review, which may jeopardize future funding. If research findings are pending publication you must still include enough detail for the expert peer reviewers to evaluate the progress during the course of the project.

Health research grants funded under the Tobacco Settlement Act will be evaluated via a performance review by an expert panel of researchers and clinicians who will assess project work using this Final Progress Report, all project Annual Reports and the project's strategic plan. After the final performance review of each project is complete, approximately 12-16 months after the end of the grant, this Final Progress Report, as well as the Final Performance Review Report containing the comments of the expert review panel, and the grantee's written response to the Final Performance Review Report, will be posted on the CURE Web site.

**There is no limit to the length of your response. Responses must be single-spaced below, no smaller than 12-point type. If you cut and paste text from a publication, be sure symbols print properly, e.g., the Greek symbol for alpha (α) and beta (ß) should not print as boxes (□) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.**

This project was developed as a new aspect of a small pilot project that previously received CURE funds. In this pilot project, we demonstrated that 1.) we can use conventional photolithography and soft lithography techniques to fabricate elastomeric, polydimethylsiloxane (PDMS) microchannels (1 cm long x 100um high x 400um wide); 2.) established hepatocyte cell lines can be maintained within the micro-environment of these channels 3.) primary rat hepatocytes and liver sinusoidal endothelial cells (LSECs) can be maintained in these microchannels; 4.) standard protein assays such a western analyses can detect various proteins from the small number (approximately 5000-8000) of hepatocytes in each microchannel; 5.) the differentiation status of hepatocytes and LSEC can be directly demonstrated by conducting reverse transcriptase-polymerase chain reaction (RT-PCR) to detect differentiation-specific mRNA markers; 6.) hepatocytes within the microchannels can be transfected with DNA or infected with recombinant adenoviruses that express a protein of interest; and 7.) layers of co-

cultured hepatocytes and an established endothelial cell line can be generated and maintained in the microchannels. We also outlined a series of conformations that would be constructed to eventually generate a novel mini-liver system that could mimic the microarchitecture and microfluidic environment of the most fundamental unit of the liver, which we have called a liver sinusoid functional unit. A schematic of the proposed mini-liver system, including various configurations that would be tested, is shown in Figure 1.

At the end of the pilot project, we had begun to construct access portals for attachment of tubing that would be linked to a mini-circulation system (Figure 1, right panel) for maintenance of constant fluid and oxygen flow in the microchannels. These microchannels with various access portal systems are shown in Figure 2. We ended the pilot project by beginning to construct methods of fluid and oxygen delivery. The *specific aims* of the project funded through the current grant were:

Aim 1: Optimize parameters for generating layered co-cultures of hepatocytes and LSECs in microchannels that are linked to microfluidic pumps so as to recreate the microenvironment of the basic functional unit of the liver.

Aim 2: Determine the cellular responses of LSECs and hepatocytes in the mini-liver system to Ritonavir.

*Addition of entry portals to the microchannels*: We first focused on continuing to optimize the microchannel portal for attaching fluid tubing. This process is complex as the portal of entry must be continuous with the microchannel, facilitate attachment of tubing for fluid circulation, form a tight, non-leaking seal that can withstand pressure associated with dynamic fluid flow (currently 0.9 μl/min.), and be constructed under sterile conditions. Our first attempt to add portals is shown in Figure 2B. In this attempt, we added an additional layer of PDMS at entry and exit sites of the microchannel. This system allowed for attachment of tubes, but fluid leakage occurred at the junction between the two membranes. In addition, it was extremely difficult to load cells through this extra layer into the microchannels as the opening did not allow for easy insertion of loading pipettes. We therefore attached short tubes to the channel opening. The final prototype of these attempts is shown in Figure 2C and D. This configuration facilitated easy loading of cells through the short tubes and can be directly connected to circulation tubes.

In an effort to combine the microchannel system directly to tubes that allow for fluid flow and oxygenation, we decided to bond the microchannels directly to glass rather than the original proposal for bonding to plastic. In this procedure, glass plates were generated, and the PDMS membrane was permanently bonded to the glass (Figure 2C). This permanent bonding can withstand the force of fluid flow, and no leakage was apparent. Because hepatocytes adhere to collagen-coated surfaces, in the original prototype we collagen-coated the tissue culture plate and then placed the microchannel on this surface; however, the use of a glass surface and permanent bonding required the development of a new protocol for collagen-coating the microchannel. Coating had to be accomplished after the channel was formed because collagen coating of the entire glass surface prevented permanent bonding of the PDMS membrane to the glass. We successfully developed methods for infusing the microchannel with collagen, allowing coating of the glass surface, and then infusing cells. Successful incorporation of HepG2 cells, a human hepatoblastoma cell line that we use as a test cell line before assaying the utility of each parameter with primary hepatocytes, demonstrated that we were able to collagen coat the microchannel surfaces.

*Optimizing co-culture of primary rat hepatocytes (PRH) and liver sinusoidal endothelial cells (LSEC)*: We previously reported identification of conditions for maintenance of PRHs and LSECs in microchannels but discovered that PRH growth medium was not compatible for LSECs and vice versa. Consequently, we redefined growth medium conditions that allows co-culture of PRHs and LSECs and confirmed that cell-specific mRNA were expressed under these conditions. Confirmation was by RT-PCR of isolated mRNAs. The medium contains all the components of our basic hepatocyte mediums (insulin, selenium, transferrin, epithelial growth factor and antibiotics) as well as 10% fetal bovine serum. It is currently unclear precisely what factors are provided in the serum, but this medium is compatible with both PRHs and LSECs. In addition, because of continual contamination of LSECs with a low level of other liver cell types and debris from the liver perfusion, we previously were forced to culture LSECs in macroscale systems, remove contaminants, and then add the LSECs to microchannels. We have now developed protocols for generating highly purified LSECs that can be directly seeded into microchannels (Figure 4). We have also developed methods for layering the LSECs over PRHs that are already seeded and have formed monolayers in microchannels. For this, we defined conditions for overlaying the PRHs with a thin layer of collagen. Specifically, we added collagen diluted in 0.15 mM Hepe buffer to the microchannel containing a monolayer of PRHs, waited 1.5 hours, washed away the collagen and then added LSECs. We have successfully co-cultured LSECs and PRHs as well as generated layered co-cultures in which matrigel or collagen is layered between the cells (Figure 5).

*$O_2$ simulation models*: The $O_2$ concentration decreases from inlet to outlet of a sinusoid; the approximate $O_2$ gradient spans from ~.084 mol/m$^3$ to ~.03 mol/m. In order to determine the feasibility of this type of $O_2$ gradient, numerical simulations were performed in COMSOL Multiphysics 3.5a using the convection/diffusion and the incompressible Navier Stokes modules; the governing equations are Navier Stokes equation and Fick's Second Law of Diffusion. For single microchannels, we simulated a polydimethylsiloxane (PDMS) microchannel with PRHs at the bottom of the channel. A parabolic flow profile was defined with a mean velocity of $1x10^{-4}$ m/s. The medium was assumed to be oxygenated to 0.084 mol/m$^3$. The $O_2$ uptake rate of PRHs, the diffusion coefficients of $O_2$ through PDMS and medium, and the distribution constant between $O_2$ in air and PDMS were obtained from the literature. The results showed that the $O_2$ diffusion through PDMS causes the $O_2$ concentration of the flowing medium to change to a steady state value at the bottom of the channel (Figure 6). This results in a smaller concentration gradient than is seen in the body, suggesting that we may have to alter our fluid flow and oxygen flow rates in the future to achieve a physiologically relevant gradient. To validate the COMSOL software, we compare our COMSOL simulation result with two existing models in the literature: Allen (2005) and Mehta (2007) (see Figures 6 and 7 for references). We first employed the mathematical model by Allen (2005) assuming uniform velocity in the whole channel and steady-state. Our boundary conditions and governing equations are the same as Allen's model. The cell uptake rate is assumed to be constant through the channel. The result in Figure 6 shows that oxygen level is decreasing smoothly along the channel, which is similar to Allen's result.

To compare with Metha's simulation (2007), a parabolic flow profile is assumed. The cell uptake rate is simulated by the Michaelis-Menten kinetic model. Oxygen diffuses from the atmosphere to the channel through the PDMS membrane. Oxygen concentration at the outlet is presented in Figure 7. This result shows good agreement with Metha's simulation.

For dual microchannels, the simulation geometry had two flow channels separated by a 10-µm thick membrane on which cells are cultured. The simulation was modeled in a similar fashion as described above with proper boundary conditions at the interfaces between materials; however, the flow is provided in different directions. Initial results showed that both channels have a similar $O_2$ concentration profile with both quickly decreasing to a concentration of about 0.077 mol/m$^3$. Oxygen level in the bottom channel is lower than the oxygen level in the top channel since we assume oxygen does not diffuse from bottom into the channel. To verify results, we are currently measuring the fluorescence of an $O_2$-quenching dye, ruthenium tris dichloride hexahydrate, flowing over cells. We simulated the oxygen concentration using the COMSOL software both in a microchannel and a dual-channel system (Figure 8). Overall, these studies have helped identify oxygen flow and fluid flow parameters that will be essential to maintain physiologically relevant conditions in the final mini-liver system.

*Oxygenator Construction*: To investigate the effect of $O_2$ concentration on liver cells, we also tested the effect of various $O_2$ levels on cell viability. We cultured PRHs in 1%, 5%, or 8% $O_2$ in a hypoxia chamber. PRHs in 5% and 8% $O_2$ remained viable throughout the culture period. RT-PCR analysis was performed for the cells in 5% $O_2$ and showed that these PRHs maintained albumin and transferrin expression (data not shown). To control $O_2$ levels in the microchannels, we have constructed an oxygenator through which the medium will pass before reaching cells in the microchannel; this device will ensure that the proper amount of $O_2$ reaches cells (Figures 3 and 9). Initially, the oxygenator was intended to provide a gas mixture of 21% $O_2$, 5% $CO_2$, and 74% nitrogen at a total pressure of 1 atmosphere. For these conditions, a numerical simulation was run to test the final concentration of $O_2$ in the media flowing through the oxygenator and the time it takes to reach that final concentration. The geometry that was modeled was a 4-inch length of silicone tubing with an inner diameter of 1.5 mm and a wall thickness of 0.75 mm. The final concentration of $O_2$ was 0.0775 mol/m$^3$, slightly less than the desired value of about 0.084 mol/m$^3$. We concluded from these observations that the gas in the oxygenator will need to be pressurized to 1.08 atm to achieve the desired $O_2$ concentration and have adjusted the pressure accordingly.

*Optimizing a Continuous Perfusion System*: Once we were successful with permanent bonding of PDMS to glass and showed that fluid flow did not cause disruption of the microchannels and leakage of fluid, we then proceeded to attach the other necessary components of the prototype microchannel system. We constructed a continuous perfusion system that consists of a syringe pump, oxygenator, bubble trap, a reservoir for waste, and the microchannel (Figure 9). A syringe and silicone tubing that is filled with the culture medium is attached to a syringe pump that pumps the medium through the oxygenator and into the microchannel. An inlet and outlet for medium flow were made using syringe tips that were inserted through holes in the lid. Upon entering the oxygenator, medium travels through the silicone tubing, which allows for the $O_2$ to diffuse through to the medium; a bubble trap receives the $O_2$-rich medium from the oxygenator and sends the medium to the microchannel. Tubes were connected from a growth-medium reservoir through a peristaltic pump to an oxygenator and bubble trap and then into the intake portal of the microchannel. Again, while seemingly simple, this required testing various flow rates to ensure that bubbles did not become trapped in the tubing; air bubbles block fluid flow through the microchannels. Oxygenation is necessary because the PDMS membrane slowly becomes coated with proteins present in the cell growth medium, and this prevents diffusion of gases. An exit portal was then attached to tubing for collection into a waste container.

Alternatively, the exit fluid can also be collected for analysis of its components. The prototype microfluidic microchannel with continuous fluid flow is shown in Figure 9. The prototype was bonded to another piece of glass so that the entire device can be mounted on a microscope stage for continuous observation of the cells in the microchannels. The microchannel chambers can be removed and new ones integrated into the model. We have tested the perfusion system with RAMEC, HepG2, and PRHs. The syringe pump was started at a flow rate of 0.1 µL/min and the oxygenator was pressurized to 20 psi. We initially observed that the cells survived for only about six hours under continuous perfusion. In order to increase the $O_2$ concentration in the microchannel and decrease the shear stress, we tried various perfusion conditions, flow rates, and configurations and have increased the survival period to at least 35 hours of continuous perfusion.

Unfortunately, although primary hepatocytes also adhered to the glass surface, viability was less than on collagen-coated tissue culture plate surfaces. We proceeded to test different coating materials and methods, but hepatocyte viability was severely impaired in microchannels in which the cell-attachment surface was glass. At this stage, we decided to take a multi-pronged approach in which we redesigned our procedure for attaching the microchannels to a plastic, collagen coated surface. The ultimate goal was to design a new attachment system that could be re-introduced into the continuous perfusion system as well as the dual microchannel platforms. Although leakage from the channels was a major impediment to our progress, we have now solved this problem as described below in: *Solving the problem of microchannel leakage.*

*Fabrication of Dual Microchannel Platforms*: We have built dual microchannels to generate higher configuration platforms that simulate liver sinusoids (Figure 10). The dual channel platform consists of two PDMS microchannels with a layer of parylene in between. Before these channels were fabricated, we demonstrated that PRHs and LSECs adhere to parylene and remain viable (data not shown). The first step in the microchannel fabrication process was soft lithography to create PDMS microchannels. These microchannels were then cut out individually, and pairs of these microchannels were "sandwiched" together with a 10-µm thick layer of microporous parylene in between. We have made a slightly altered design from the previously proposed one. The previous straight microchannel design did not allow us to "sandwich" the membrane in between because the membrane would not have been able to completely separate the two channels. Also, the inlet and outlet would overlap with those microchannels, and this is not desired because potential set-ups may require that the inlet and outlet of both channels be accessible from one side. The new design has a straight channel with the same dimensions as described in the original proposal and an extra channel length at both ends that extends out at an angle so that the holes do not overlap. The two channels were attached together by $O_2$ plasma bonding. PRHs survived in this system for at least 12 days.

*Culture of primary human hepatocytes in microchannels:* A longterm goal of this project is to replace PRHs with human hepatocytes to create a novel human mini-liver system. Primary human hepatocytes were acquired from the NIDDK-sponsored liver tissue procurements system and seeded into microchannels (Figure 11). Cells were isolated from the microchannels at various times post-seeding, RNA was isolated, and RT-PCR was performed to confirm expression of albumin, transferrin, connexin 43 and 32 (hepatocyte specific markers) and the

absence of connexin 27 (markers of LSECs and Kuppfer cells, but absent from hepatocytes). Hepatocytes expressed specific markers and survived in the channels for at least 10 days.
*Solving the problem of microchannel leakage*: The major impediment to completion of the miniliver system during the final months of funding was leakage from the microchannels attached to plastic surfaces. Although the microchannels bonded to glass could withstand fluid flow rates necessary to maintain hepatocyte viability, glass was not a suitable substrate for longterm attachment and maintenance of viable, differentiated hepatocytes (described in *Optimizing a Continuous Perfusion System)*. This forced us to change the substrate that microchannels would be attached to back to plastic for subsequent incorporation into the continuous perfusion system.

We first tried to ascertain the cause of the leakage when microchannels were adhered to a collagen-coated plastic surface. Scanning electron microscopy was used to inspect the surface of the PDMS and collaged-coated petri dishes. However, the results of this inspection were inconclusive. Additionally, we performed a simple experiment to determine if the cells interacting with the edge of the microchannel might contribute to channel leakage in the context of continuous fluid flow. Instead of culturing cells in the PDMS channels laid on a collagen-coated petri dish, only culture media was pipetted into the channels and was changed twice daily to simulate the culture media change routinely performed for the cells. In this experiment, only 1 of 32 channels leaked during a 2-week period, whereas the channels with cells have had around a 75% leakage rate after a couple of days. These results may suggest that the presence of the cells in the channel could contribute to some of the leakage we have observed. In order to fix this leakage issue while not drastically altering the cell culturing set-up, several different methods were attempted. The first method that was tried was laser machining a poly(methyl methacrylate), or PMMA, plate that could be force-fit into the petri dish on top of the PDMS channels. The idea behind this concept is that with the pressure of the PMMA plate on the PDMS, the channels would be sealed off adequately. Also, the PMMA plate was machined so that there were holes in the plate in the shape of the channels; this allowed for access to the channels and prevented the blockage of oxygen diffusion to the cells. However, due to the flexibility of the petri dish, the pressure of the plate against the walls of the dish caused the bottom of the dish to bend, and the channels were never sealed off properly. Another method that was attempted involved a different method of collagen coating. Instead of collagen coating the entire petri dish, the PDMS channels were first placed on the uncoated dish, which allows for better adhesion. Then collagen was pipetted into the channel, filling it, and the collagen was allowed to settle down and attach in the channel. The collagen in the channel helped provide a seal between the edges of the channel and the dish, and consequently, these channels did not leak. Among 28 channels used in cell culture, none of them leaked after a period of 5 days. However, the cells did not attach in significant numbers in this arrangement; there were only patches of healthy cells. Finally, in order to provide a good seal between the channels and the plate, a spring-loaded mechanism has been generated (Figure 12). One part of the assembly of this mechanism requires that two small plastic pieces be glued to the walls of a collagen-coated petri dish on opposite sides. Also, two PMMA plates must be laser machined, and these two plates are then attached by four springs. Once placed in the petri dish, one plate presses against the channels, and the other plate presses up against the pieces glued to the wall of the petri dish. In this arrangement, the springs are deflected slightly, which provides a force down to the channels, properly sealing them off. As of now, 16 channels have been used for cell culture in

this arrangement, and none of them have experienced leakage. Additionally, since this method requires a similar cell-culturing set-up to one we have had previous success with, it can be incorporated into the previously designed continuous perfusion platform.

*Portions of project not yet completed:* Due to problems with leakage of the microchannels, at the end of the funding period, we had not yet progressed to Aim 2. However, we have now solved the microchannel leakage problem and because we had simultaneously tested fluid perfusion parameters, oxygen concentrations necessary for cell survival in the microchannels, methods for generating layered co-cultures of PRHs and LSECs, we are now completing the last stages of Aim 1 by incorporating the new microchannel design into the continuous perfusion system. We expect to complete this in the current year and continue with studies that test the impact of drugs and alcohol on hepatocytes maintained in this new model system.

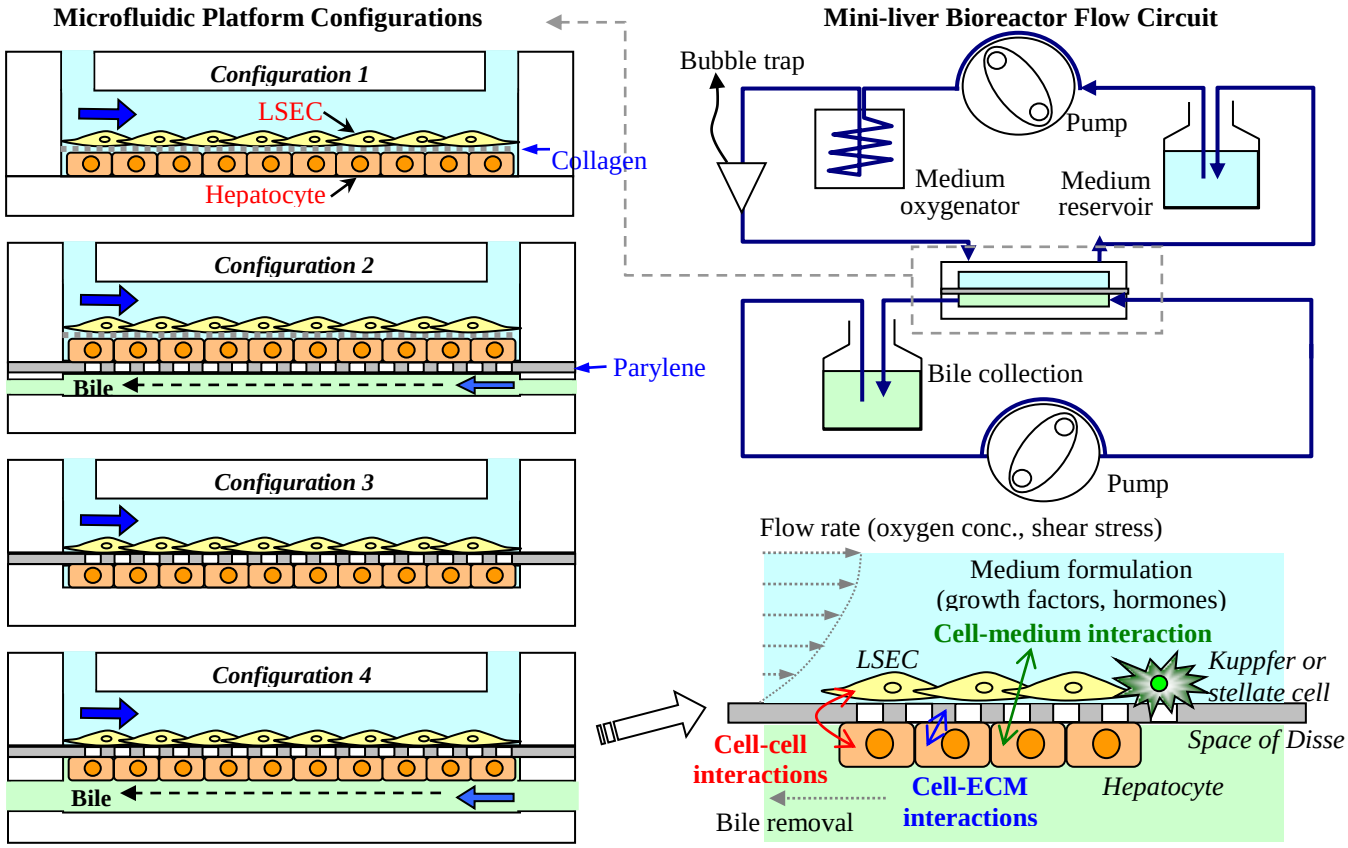



Figure 1. Schematic of proposed mini-liver bioreactor system. Microfluidic cell culture platform configurations (left) and flow circuit for continuous perfusion and bile collection (top right), and cellular microenvironment (bottom right).

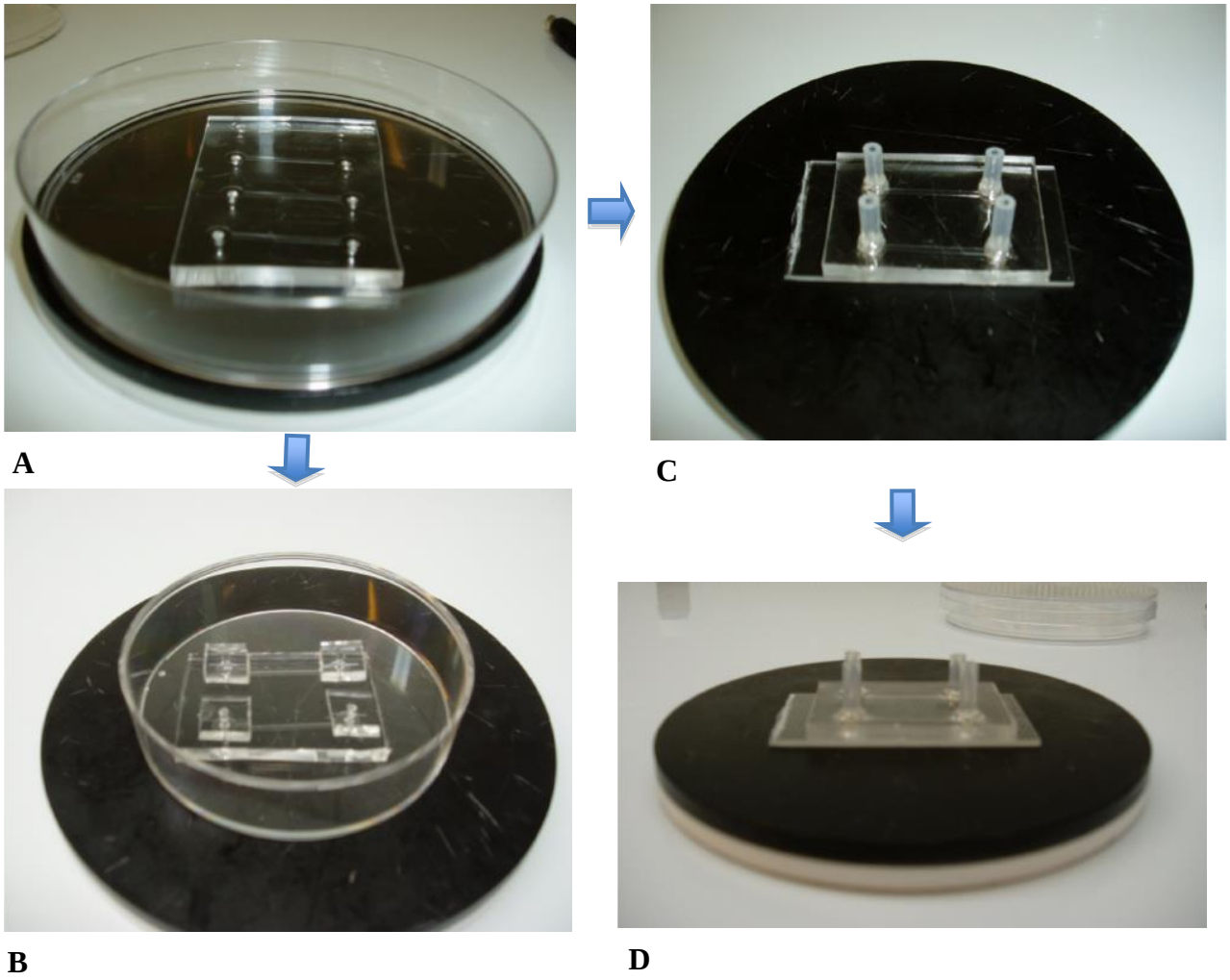
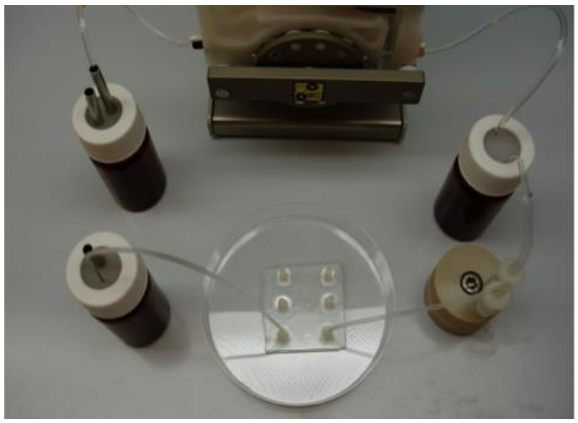
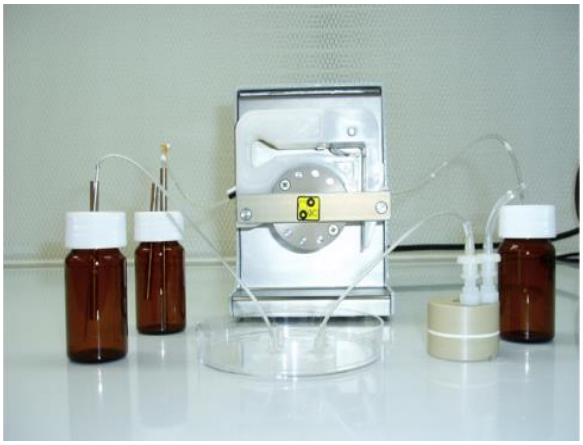


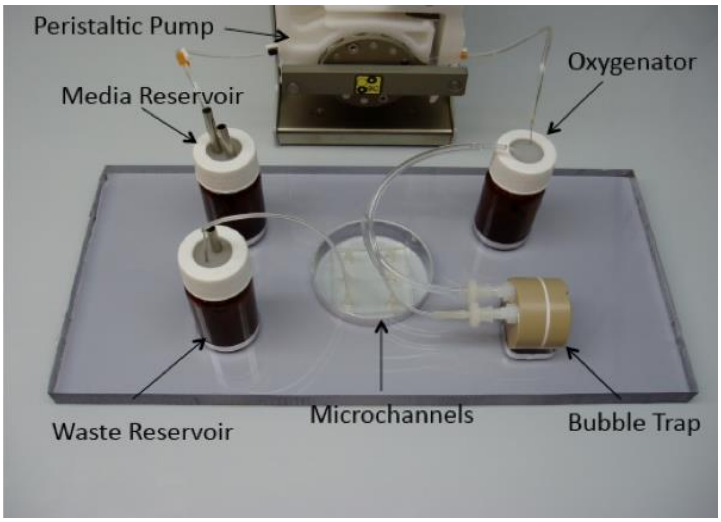

Figure 2: Design for attachment of tubing portals for dynamic flow system: A. Design of original static microchannel system. Microchannels are generated within PDMS membrane layered onto a collagen-coated tissue plastic plate. Four channels in 6cm plate are shown. B. First attempt at generating portals for tubing (see text for explanation). C and D: final design for tubing portals. Panel C is from 45° angle and Panel D is photographed from side.





**A**

**B**




**C**

Figure 3: Design of dynamic flow system. Panels A and B: dynamic flow system from top and side. Panel C: final system with labeled components. This system is attached to a glass support so that the entire system can be place on the stage of a microscope for continual observation.

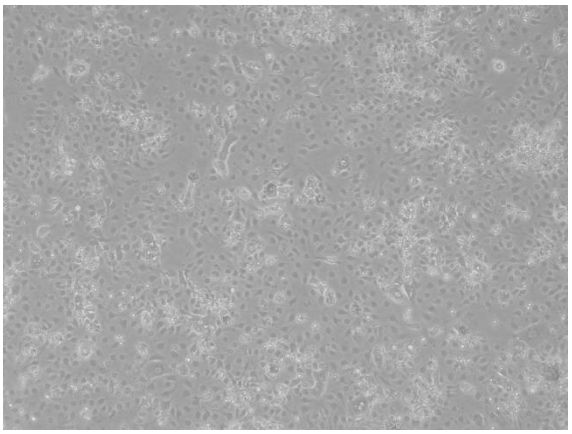


Figure 4: LSECs plated directly into microchannels. LSEC were isolated from perfused livers by differential centrifugation followed by Percoll gradient purification and direct infusion into microchannels.

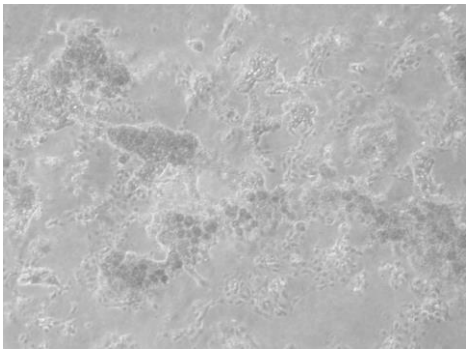
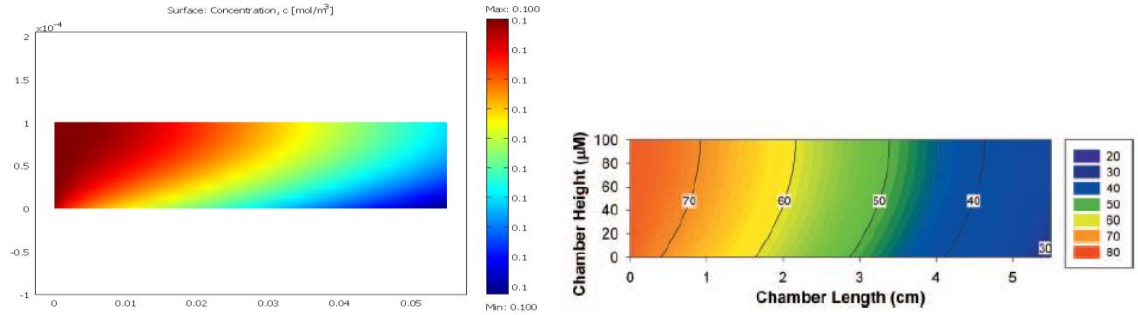
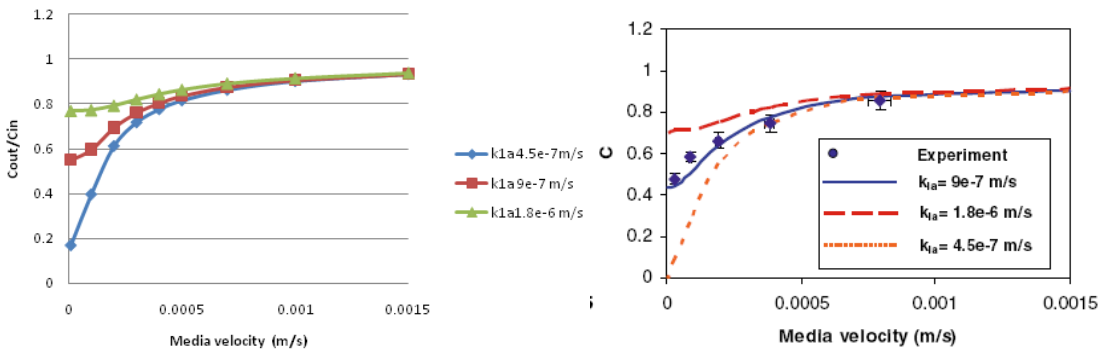


Figure 5. Layered co-culture of PRHs and LSECs. Right panel shows upper layer of hepatocytes, lower panel is refocused on lower layer of LSECs




**A.** **B.**

Figure 6. Governing Equations and Boundary Conditions in Allen's Model (2005) for modeling oxygen concentration in a microchannel. (A) Our COMSOL simulation result. Simulation parameters: width 5.5e-2 m , height 1.0e-4 m, uniform velocity 0.01 m/s, cell uptake rate 6.46e-10 mol/s/m$^2$, and initial oxygen concentration 0.1 mol/m$^3$. (B) Allen (2005) simulation result. (REF: J.W. Allen, S.R. Khetani, and S.N. Bhatia, In Vitro Zonation and Toxicity in a Hepatocyte Bioreactor, Toxicological Sciences, 84,110-119 (2005))




(A) (B)

Figure 7**.** Governing equations and boundary conditions in Metha's simulation (2007) used to calculate oxygen concentration at the outlet of the channel. Our simulation shows good agreement with Metha's simulation. (A) Our COMSOL simulation result. Simulation parameters: height 40 µm, length 0.01 m, diffusivity 2.1e-9 $m^2/s$, Vmax 2.06e-16 mol/cell/s, Km 0.005 $mol/m^3$. (B) Metha's simulation result (2007). (REF: G. Mehta, K. Mehta, D. Sud, J.W. Song, T. Bersano-Begey, N. Futai, Y.S. Heo, M. Mycek, J. J. Linderman, S. Takayama, Quantitative Measurement and Control of Oxygen Levels in Microfluidic Poly(dimethylsiloxane) Bioreactors During Cell Culture, Biomed Microdevice 9: 123-134 (2007). )

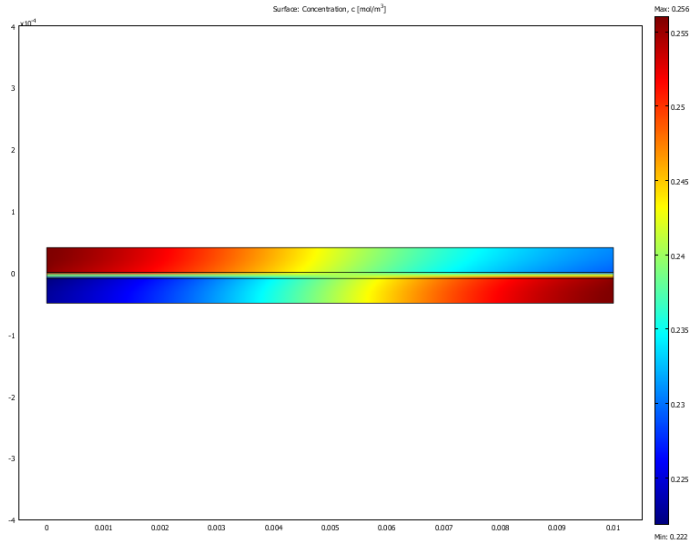


Figure 8**.** Oxygen concentration in a dual channel. Simulation parameters: height 40 µm, length 0.01 m, diffusivity of PDMS 2.1e-9 $m^2/s$, Vmax 2.06e-16 mol/cell/s, Km 0.005 $mol/m^3$, thickness of the membrane is 10 µm, and diffusivity of the membrane is 2.09e-13 $m^2/s$.

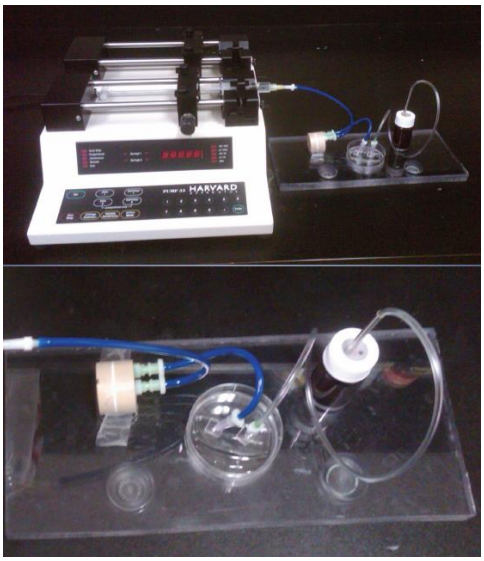



Figure 9: Continuous perfusion system. A syringe pump (upper panel) was attached to the microchannel system and various flow rates were tested to identify the flow rate that facilitated cell survival. See text for description of system and test of parameters.

Figure 10: Fabrication of dual microchannel. See text for description.

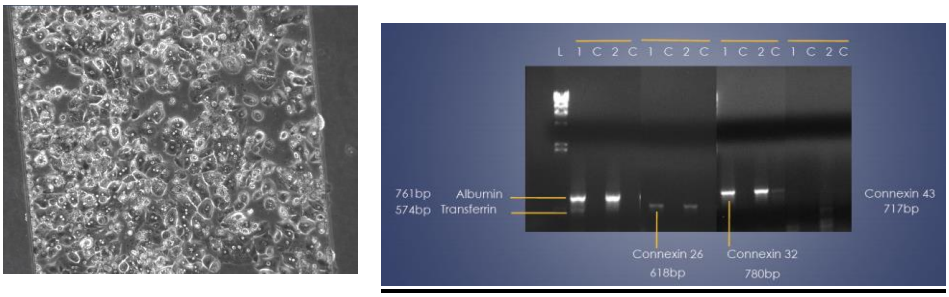



Figure 11: Primary human hepatocytes in microchannels. Right panel, cultured primary human hepatocytes in microchannels. Left panel, confirmation of expression of liver specific mRNAs by RT-PCR (see text for details).

Figure 12: New spring-loaded microchannel device to prevent leakage. See text for details.

**18. Extent of Clinical Activities Initiated and Completed**. Items 18(A) and 18(B) should be completed for all research projects. If the project was restricted to secondary analysis of clinical data or data analysis of clinical research, then responses to 18(A) and 18(B) should be "No."

18(A) Did you initiate a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
__X___No

18(B) Did you complete a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
____X_No

**If "Yes" to either 18(A) or 18(B), items 18(C) – (F) must also be completed.** (Do NOT complete 18(C-F) if 18(A) and 18(B) are both "No.")

18(C) How many hospital and health care professionals were involved in the research project?

_____Number of hospital and health care professionals involved in the research project

18(D) How many subjects were included in the study compared to targeted goals?

_____Number of subjects originally targeted to be included in the study
_____Number of subjects enrolled in the study

18(E) How many subjects were enrolled in the study by gender, ethnicity and race?

Gender:
_____Males
_____Females
_____Unknown

Ethnicity:
_____Latinos or Hispanics
_____Not Latinos or Hispanics
_____Unknown

Race:
_____American Indian or Alaska Native
_____Asian
_____Blacks or African American
_____Native Hawaiian or Other Pacific Islander
_____White
_____Other, specify:_____
_____Unknown

18(F) Where was the research study conducted? (List the county where the research study was conducted. If the treatment, prevention and diagnostic tests were offered in more than one county, list all of the counties where the research study was conducted.)

**19. Human Embryonic Stem Cell Research.** Item 19(A) should be completed for all research projects. If the research project involved human embryonic stem cells, items 19(B) and 19(C) must also be completed.

19(A) Did this project involve, in any capacity, human embryonic stem cells?
_____Yes
__X__ No

19(B) Were these stem cell lines NIH-approved lines that were derived outside of Pennsylvania?
_____Yes
_____ No

19(C) Please describe how this project involved human embryonic stem cells:

**20. Articles Submitted to Peer-Reviewed Publications**.

20(A) Identify all publications that resulted from the research performed during the funding period and that have been submitted to peer-reviewed publications. Do not list journal

abstracts or presentations at professional meetings; abstract and meeting presentations should be listed at the end of item 17. **Include only those publications that acknowledge the Pennsylvania Department of Health as a funding source** (as required in the grant agreement). List the title of the journal article, the authors, the name of the peer-reviewed publication, the month and year when it was submitted, and the status of publication (submitted for publication, accepted for publication or published.). Submit an electronic copy of each publication, listed in the table, in a PDF version 5.0.5 format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, the number of the publication and an abbreviated research project title. For example, if you submit two publications for PI Smith for the "Cognition and MRI in Older Adults" research project (Project 1), and two publications for PI Zhang for the "Lung Cancer" research project (Project 3), the filenames should be:

Project 1 – Smith – Publication 1 – Cognition and MRI
Project 1 – Smith – Publication 2 – Cognition and MRI
Project 3 – Zhang – Publication 1 – Lung Cancer
Project 3 – Zhang – Publication 2 – Lung Cancer

If the publication is not available electronically, provide 5 paper copies of the publication.

**Note:** The grant agreement requires that recipients acknowledge the Pennsylvania Department of Health funding in all publications. Please ensure that all publications listed acknowledge the Department of Health funding. If a publication does not acknowledge the funding from the Commonwealth, do not list the publication.

| Title of Journal Article: | Authors: | Name of Peer-reviewed Publication: | Month and Year Submitted: | Publication Status (check appropriate box below): |
|---|---|---|---|---|
| 1. None | | | | ☐Submitted<br>☐Accepted<br>☐Published |

20(B) Based on this project, are you planning to submit articles to peer-reviewed publications in the future?

Yes_____X____ No_____

If yes, please describe your plans:

We plan a minimum of two publications from the work funded by this grant. In one publication, we will describe the final micro-fabricated mini-liver system, the specifics of its construction, and describe our confirmation of the maintenance of cell specific functions and phenotypes. In the second publication, we will describe our studies regarding control of oxygen levels and fluid flow within the microchannels and the effect of these parameters of cell survival and cell specific functions. We believe that this information will be useful to others attempting similar models and will serve as the foundation for our future expansion of this model system and the demonstration of its utility of a novel model for studying liver biology.

**21. Changes in Outcome, Impact and Effectiveness Attributable to the Research Project.** Describe the outcome, impact, and effectiveness of the research project by summarizing its impact on the incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of outcome, impact or effectiveness of the research project. If there were no changes, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

None

**22. Major Discoveries, New Drugs, and New Approaches for Prevention Diagnosis and Treatment**. Describe major discoveries, new drugs, and new approaches for prevention, diagnosis and treatment that are attributable to the completed research project. If there were no major discoveries, drugs or approaches, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

None

**23. Inventions, Patents and Commercial Development Opportunities.**

23(A) Were any inventions, which may be patentable or otherwise protectable under Title 35 of the United States Code, conceived or first actually reduced to practice in the performance of work under this health research grant? Yes_____ No___X_____

If "Yes" to 23(A), complete items a – g below for each invention. (Do NOT complete items a - g if 23(A) is "No.")

a. Title of Invention:

b. Name of Inventor(s):

c. Technical Description of Invention (describe nature, purpose, operation and physical, chemical, biological or electrical characteristics of the invention):

d. Was a patent filed for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No___

If yes, indicate date patent was filed:

e. Was a patent issued for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No___
If yes, indicate number of patent, title and date issued:
Patent number:

Title of patent:
Date issued:

f. Were any licenses granted for the patent obtained as a result of work performed under this health research grant? Yes_____ No____

If yes, how many licenses were granted?_____

g. Were any commercial development activities taken to develop the invention into a commercial product or service for manufacture or sale? Yes___ No____

If yes, describe the commercial development activities:

23(B) Based on the results of this project, are you planning to file for any licenses or patents, or undertake any commercial development opportunities in the future?

Yes_____X____ No_____

If yes, please describe your plans:

Once the entire microfluidic liver platform is complete, we will patent the design and construction. We have also discussed with two local companies, Merck and Medical Diagnostic Laboratories (MDL), the possibility of using this system in their drug testing schemes with the longterm goal of commercializing this technology as a method for testing drug toxicity in a human liver system that should accurately reflect the consequence of drug treatment within the whole liver. We recognize that this system will not include an inflammatory response but believe that it will still provide a more accurate human liver model for testing drug toxicity than the currently available systems.

**24. Key Investigator Qualifications.** Briefly describe the education, research interests and experience and professional commitments of the Principal Investigator and all other key investigators. In place of narrative you may insert the NIH biosketch form here; however, please limit each biosketch to 1-2 pages. *For Nonformula grants only – include information for only those key investigators whose biosketches were not included in the original grant application.*

## Biographical Sketches

| NAME<br>Michael J. Bouchard | POSITION TITLE<br>Associate Professor<br>Dept. of Biochemistry and Molecular Biology |
|---|---|

EDUCATION/TRAINING

| INSTITUTION AND LOCATION | DEGREE *(if applicable)* | YEAR(s) | FIELD OF STUDY |
|---|---|---|---|
| Cornell University | B.S. | 1987 | Microbiology |
| Columbia University | M.A. | 1989 | Microbiology |
| Columbia University | M. Phil. | 1990 | Microbiology |
| Columbia University | Ph.D. | 1997 | Microbiology |

**POSITIONS AND HONORS:**

**Positions:**

1989-1996 **Graduate Student**, Dept. of Microbiology, Columbia University. Thesis Advisor: Dr. Vincent Racaniello.

1997-2003 **Post-doctoral fellow**, Dept. of Microbiology, New York University School of Medicine. Mentor: Dr. Robert Schneider.

2004-2010. **Assistant Professor**, Dept. of Biochemistry and Molecular Biology, Drexel University College of Medicine, Philadelphia, PA.

2010-pres. **Associate Professor**, Dept. of Biochemistry and Molecular Biology, Drexel University College of Medicine, Philadelphia, PA.

2007-pres. **Director**, Graduate Program in Molecular and Cellular Biology and Genetics, Drexel University College of Medicine, Philadelphia, PA

**PEER-REVIEWED PUBLICATIONS (limited to 12):**

M. Bouchard, L-H. Wang, and R. Schneider. (2001) Calcium signaling by HBx protein in Hepatitis B virus DNA replication. ***Science*** 294: 2376-2378. PMID: 11743208

M. Bouchard, R. Puro, L-H. Wang, and R. Schneider. (2003) Activation and inhibition of cellular calcium and tyrosine kinase signaling pathways identify targets of the HBx protein involved in HBV replication. ***J Virol.*** 77: 7713-7719. PMID: 12829810

M. Bouchard, L-H. Wang, and R. Schneider. (2006) Activation of focal adhesion kinase by Hepatitis B virus HBx protein: multiple functions in viral replication. ***J. Virol*** 80; 4406-4414. PMID: 16611900

S. McClain, A. Clippinger, R. Lizzano and M. Bouchard. (2007) HBV replication is associated with an HBx-dependent mitochondrion-regulated increase in cytosolic calcium levels. ***J. Virol*** 81; 12061-12065. PMID: 17699583

T. Sodunke, M. Bouchard and H. Noh (2008) Microfluidic platform for hepatitis B viral replication study. ***Biomed Microdevices*** 10: 393-402. PMID: 18165913

A. Clippinger and M. Bouchard. (2008) The hepatitis B virus HBx protein localizes to mitochondria in primary rat hepatocytes and modulates mitochondria membrane potential. ***J. Virol*** 82; 6798-6811. PMID: 18448529

A. Clippinger, T. Gearhart and M. Bouchard. (2009) The hepatitis B virus X protein modulates apoptosis in primary rat hepatocytes by regulating both NF-□B and the mitochondrial permeability transition pore. ***J. Virol.*** 83: 4718-4713. PMID: 19279112

EA Vitol, Z. Orynbayeva, M. Bouchard, J. Azizkhan-Clifford, G. Friedman, and Y. Gogotsi. (2009) *In situ* intracellular spectroscopy with surface enhanced raman spectroscopy (SERS)-enabled nanopipettes. ***ACS Nano.*** 3; 3529-3536. PMID: 19891490

T. Gearhart and M. Bouchard. (2010) The hepatitis B virus X protein modulates hepatocyte proliferation pathways to stimulate viral replication. ***J. Virol***. 84: 2675-2686. PMID: 20053744

T. Gearhart and M. Bouchard. (2010) Replication of the Hepatitis B Virus Requires a Calcium-Dependent HBx-Induced G1 Phase Arrest of Hepatocytes. ***Virology*** 407: 14-25, PMID: 20719353.

T. Gearhart and M. Bouchard. (2011) The hepatitis B virus HBx protein modulates cell cycle regulatory proteins in cultured primary human hepatocytes. ***Virus Res.*** 155: 363-367. PMID: 20934470.

R. Lizzano, B. Yang, A. Clippinger, and M. Bouchard. (2011) The C-terminal region of the hepatitis B virus X protein is essential for its stability and function. ***Virus Res.*** 155: 231-239. PMID: 20969903.

**RESEARCH SUPPORT:**

**Ongoing Research Support:**

Project Title: **The role of hepatitis B virus X protein in viral replication.**
Sponsor: 5R01AI64844, NIH-NIAID
Project Period: 12/2005 – 11/2011
P.I.: Michael Bouchard

The goal of this project is to define the molecular mechanisms that underlie the activities of the hepatitis B virus X protein during HBV replication and their impact on hepatocellular physiology.

Project Title : **A Microfluidic-platform Mini-Liver System for Human Liver Biology Studies**.
Sponsor : NIH/NIAAA R21 AA017458-01A2
Project period: 8/20/09 – 07/31/11
MPI : Michael Bouchard and Moses Noh

This goal of this grant is to develop a novel human liver model in which human liver cells are co-cultured in microchannels so as to mimic the microenvironment of a liver sinusoid. Once established, the impact of alcohol exposure and HBV infections on hépatocyte physiology will be tested.

| NAME | POSITION TITLE |
|---|---|
| **Hongseok (Moses) Noh** | Associate Professor, Mechanical Engineering |
| eRA COMMONS USER NAME (credential, e.g., agency login) | Director, Drexel Lab-on-a-Chip and BioMEMS Lab. |
| Mosesnoh1 | |

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

| INSTITUTION AND LOCATION | DEGREE *(if applicable)* | YEAR(s) | FIELD OF STUDY |
|---|---|---|---|
| Korea University, Seoul, Korea | B.S. | 1994 | Material Sci. and Eng. |
| Korea University, Seoul, Korea | M.S. | 1996 | Material Sci. and Eng. |
| Georgia Institute of Technology | Ph.D. | 2004 | Mechanical Engineering |
| Georgia Institute of Technology | Postdoc. | 2004 | Mechanical Engineering |

## Positions and Honors

**Positions and Employment**

2010 – Present Associate Professor, Mechanical Engineering and Mechanics, Drexel University

2004 – 2010 Assistant Professor, Mechanical Engineering and Mechanics, Drexel University

2004 – present Director, Lab-on-a-Chip and BioMEMS Laboratory, Drexel University

**Other Experience and Professional Memberships**

2000-present Member, American Society of Mechanical Engineers (ASME)

2000-present Member, Institution of Electrical and Electronics Engineers (IEEE)

**Honors**

2008 National Science Foundation (NSF) CAREER Award

## Selected Peer-reviewed Publications (limited to 5 related to project)

1. T. R. Sodunke, K. K. Turner, S. A. Caldwell, K. W. McBride, M. J. Reginato, and H. Noh, "Micropatterns of Matrigel for Three-Dimensional Epithelial Cultures." *Biomaterials*, Vol 28/27, 4006-4016, 2007
2. T. Sodunke, M. Bouchard, and H. Noh, "Microfluidic Study for Hepatitus B Viral Replication Study," *Biomedical Microdevices*, Vol. 10, No. 3, 393-402, 2008.
3. H. Noh, Y. Huang, and P. J. Hesketh, "Parylene Micromolding, a Rapid and Low-Cost Fabrication Method of Parylene Microchannel." *Sensors and Actuators B,* Vol. 102, 78-85, 2004.
4. R. Luharuka, H. Noh, S. Kim, and P. J. Hesketh, "Improved Manufacturability and Characterization of a Corrugated Parylene Diaphragm Pressure Transducer." *Journal of Microengineering and Micromechanics*, Vol. 16, 1468-1474, 2006.
5. J. Oh, R. Hart, J. Capurro, and H. Noh, "Comprehensive analysis of particle motion under non-uniform AC electric fields in a microchannel," *Lab Chip*, Vol. 9, 62-78, DOI:10.1039/ B801594E, 2009.

## Research Support

Project title: **CAREER: Engineering a Liver Sinusoid Functional Unit**
Sponsor: NSF CBET #0747752, Project period: 4/15/08-4/14/13, PI: Hongseok (Moses) Noh

The goal of this project is to develop an authentic human liver model by combining microfabrication, microfludics technologies with cell culture technology. A layered co-culture of hepatocytes and endothelial cells in microchannles that simulates the sinusoid and bile duct will be generated and tested in regard to liver-specific functions. If successful, this project will produce an authentic liver model/bioreactor that can be used for a variety of liver biology studies and drug screening applications.

Project title: **Implantable Microdevice for the Treatment of Hydrocephalus**
Sponsor: NIH/NINDS 1 R21 NS057474-01A2, Project period: 9/01/08-8/31/11, PI: Hongseok (Moses) Noh
The goal of this project is to develop and test an implantable microdevice for the treatment of hydrocephalus. The proposed device that consists of microneedle and microvalve arrays closely mimics the function of natural arachnoid villi. If successful, this project will produce a new treatment for hydrocephalus, overcoming most of the shortcomings of the current treatment (shunt systems).

Project title: **A Microfluidic-platform Mini-Liver System for Human Liver Biology Studies**
Sponsor: NIH/NIAAA 1R21AA017458-01A2, Project period: 9/1/2009-8/31/2011, PIs: Hongseok (Moses) Noh and Michael Bouchard
The specific aims of this project are: 1) To develop a novel “mini-liver” culture system using a microfluidic platform that simulates a liver sinusoid functional unit, and 2) To test the utility of this system with focused studies that analyze the effect of Hepatitis B virus (HBV) replication and alcohol exposure on specific hepatocyte signaling pathways.

Project title: **MRI: Acquisition of 3-D Micromanufacturing Instruments for Bioengineering Research at Drexel University**
Sponsor: NSF CBET #0923173, Project period: 9/1/2009-8/31/2011, PI: Hongseok (Moses) Noh
The goal of this project is to improve the quality and expand the scope of bio-engineering research and training at Drexel University by providing shared 3-D micromanufacturing instrumentation. This proposal seeks the acquisition of two complementary 3-D micro-manufacturing instruments: *a micro stereolithography system* and *an excimer laser ablation system*.

Project title: **Micro-Fluidic Laboratory (MFL) Modules and Kits for Undergraduate Education (Type 2)**
Sponsor: NSF DUE #1022757, Project period: 9/1/10-8/31/13, PI: Hongseok (Moses) Noh

This project builds on the success in Type 1 project with the same title. The goal is to develop and test new sets of experimental modules and kit for microfluidics education of undergraduate students. Five institutions including Drexel are involved in this project. If successful, new sets of microfluidics laboratory kits will be developed and commercialized for broader dissemination across the nation to improve undergraduate education and research activities.

Project title: **Upgrade and Renovation of Drexel Microfabrication Facility**
Sponsor: NSF DUE #0963319, Project period: 10/1/10-9/30/13, PI: Hongseok (Moses) Noh

The goal of this project is to upgrade and renovate Drexel's centralized Microfabrication Facility (MFF). The project includes expansion of gowning/maintenance area, upgrading the labs to class 100 cleanroom, and lab furniture replacement. Once completed, the renovated MFF will benefit a broad spectrum of Drexel research community and beyond.